If specific reliability performance claims are not intended, the documentation outlined in the GMP requirements are sufficient. In this case, submission in the original Investigational Device Exemption (IDE) application and periodic update/revision of a FMECA is recommended.

10. Arrhythmia Detection Performance Testing

Prior to any clinical evaluation, conduct performance testing of the arrhythmia detection algorithm. Simulated and actual human recorded arrhythmias from a database of intracardiac electrograms may be used to evaluate the detection and therapy delivery of the ICD. Play the arrhythmias into the sample devices as if they were implanted and receiving signals from the actual leads. Design and develop the arrhythmia detection algorithm using a database (the *training set*) that is different from the set used to verify the performance of the arrhythmia detection algorithm *(the test set)*.

At present, a common database created from actual lead recordings is not available for ICD testing; nor is there a set of recommended practices or standard procedures for testing and validating the arrhythmia detection algorithms. In characterizing the database, it is important to describe information such as the type of arrhythmia, the number of patients, the number of arrhythmia episodes per patient, the duration of arrhythmia episodes, the leads used to obtain the cardiac signals, etc. A discussion of the signal processing techniques, data acquisition methodology, and other relevant parameters will also provide practical information.

In reporting the results of the arrhythmia detection performance testing, include a description of the test protocol, a discussion of the sources of error, and a summary of the test results (sensitivity and specificity). Program the device under test using all detection zones and detection enhancements when testing the algorithm for tachycardia recognition.

This information will be helpful in the process of interpreting premarket clinical data.

B. Software

The information submitted for software (or firmware) documentation and performance for ICDs and their programmers should be consistent with the current *ODE Guidance for the Scientific Review of Premarket Medical Device Software Submissions* [2]. This information should include software development/environment, software/system requirements, software and system hazards analysis, and software verification and validation information.

C. Biocompatibility

The overall safety evaluation of the investigational device begins with an assessment of its biocompatibility. Biocompatibility evaluation depends, in part, on the full characterization of all device materials after sterilization. It is important to identify leachables, by products and metabolites which may pose a threat to the health and well being of the patient. This is accomplished by using appropriate extraction methods and laboratory procedures to analyze the chemical and physical components of the device. Protocols, test results, and control materials used in the assessment of device biocompatibility should be provided in the IDE application in order to facilitate the independent evaluation of device biocompatibility.

For a device material which has been tested and used previously in direct blood contact devices, a sponsor may submit information available in publications or other legitimate sources which show that the material is nontoxic in tests identical or equivalent to the biological tests outlined in the Blue Book Memorandum # G-95-1 [3]. All new materials in the non-hermetic portion of the device

should pass the tests below to insure safety for use in permanent implants. Protocols do not need to be submitted if standard testing methods are utilized (e.g., USP methods) and complete references for the methods are provided.

Specific chemical analyses of the sterilized final product, and any leachable material from the sterilized final product, should be performed before initiating toxicity testing. Furthermore, the tests and analyses for leachable materials should be conducted by choosing appropriate solvent systems which will yield a proper extraction of the leachables.

Necessary toxicity tests. The following biocompatibility tests are considered necessary and appropriate based upon device use and mode of contact with the body. Other tests may be required, depending upon the nature of the device material. If a test is omitted, or a substitute test is provided, the manufacturer should provide adequate justification for this action. All chemical analyses and toxicity data should be submitted to the FDA for review.

a. Acute Systemic Toxicity: To estimate the effects of either single or multiple exposures to test materials and/or extracts, in an animal model, during a period of less than 24 hours. (Ref. USP Systemic Injection Test).

b. Irritation Tests: To estimate the irritation and sensitization potential of test materials and their extracts, using appropriate site or implant tissue such as skin and mucous membrane in an animal and/or human model. (Ref. USP Intracutaneous Test).

c. Implantation Tests: To evaluate the local toxic effects on living tissue, at both the gross and microscopic level, from a sample material that is surgically implanted into the appropriate animal implant site or tissue, e.g. muscle, for 7-90 days. (Ref. USP Implantation Test).

d. Sensitization Assay: To estimate the potential for sensitization to a test material and/or material extracts using an animal and/or human model. (Ref. Guinea Pig Maximization Test or human patch test).

e. Cytotoxicity: To determine the lysis of cells (cell death), the inhibition of cell growth, and other toxic effects on cells caused by materials and/or material extracts using cell culture techniques. (Ref. MEM Elution or Agarose Overlay).

f. Hemocompatibility or Hemolysis: To evaluate the effects of blood contacting materials on hemolysis (i.e. the degree of red cell lysis and the separation of hemoglobin caused by test materials and/or *in vitro* extracts), thrombolysis, plasma proteins, enzymes, and the formed elements of blood using an animal model, with particular attention paid to the acceleration of intravascular thrombosis.

g. Pyrogenicity: To evaluate the material-mediated pyrogenicity of the test materials and/or extracts. (Ref. USP Rabbit Pyrogenicity Tests or Limulus Amebocyte Lysate (LAL)).

h. Mutagenicity or Genotoxicity: To determine gene mutations, changes in chromosome structure and number, and other DNA or gene toxicities caused by materials and/or material extracts using mammalian and normally accepted by the scientific community should be used. (Ref. AMES Mutagenicity Test).

i. Carcinogenicity: To assess the material mediated carcinogenicity of the test material and/or extract in an animal model.

D. Animal Testing

In vivo animal studies, when required, should be designed to approximate closely the intended use of the device in humans in order to demonstrate safety of the procedure, to evaluate the functional characteristics of the device design and to evaluate the performance of ICDs [4-6]. The size and duration of the animal study should parallel the extent of the clinical studies summarized on Table 1: with novel ICD designs involving larger studies; and modifications to existing designs involving smaller acute studies. Sponsors are encouraged to consult with FDA before initiating their studies for clarification of their device's category on Table 1.

1. General Considerations

a. In testing of ICD systems, the emphasis would be on testing safety and on the technical aspects of implantation, *e.g.*, safety and ease of implantation. To test ease of implantation an animal model should be selected for its resemblance to human cardiovascular system and similarity in size. For safety, the animal tests should encompass the full range of shock strengths, waveforms, shock combinations, and electrodes for intended use. For devices in which testing the number of possible therapies is both onerous and of little scientific value, the most risky combinations (*e.g.*, highest power, smallest electrodes) need be evaluated.

b. *In vitro* testing may be used as supplemental proof (not as primary evidence) of safety and efficacy.

c. Animal testing may not be required for every new system introduced unless there are significant design changes and/or new claims are being made. In these instances, the sponsor should provide adequate justification for not performing *in vivo* animal testing, if such is not done.

d. When suitable animal models to test efficacy of ICD systems are not easily available (e.g., models of atrial fibrillation), such studies should be aimed primarily at testing safety issues and ease of implantation and other technical considerations.

e. Studies should include evaluation of both short (days) and long (months) term implantation with periodic testing when appropriate, *e.g.*, epicardial patches may be prone to fibrosis and may lead to increased defibrillation threshold with time.

f. Adequate justification should be provided when parts of a system are tested rather than the complete system.

2. Post Procedure Studies

a. Complete autopsies should be performed on test animals as appropriate. Detailed pathological studies (gross and microscopic) of the heart (including the pericardium), lungs and the mediastinal structures of test animals are required.

b. Proof of safety should include direct and indirect evidence demonstrating absence of significant cardiovascular damage. Direct evidence of related damage would include death and/or tissue necrosis. Indirect evidence for damage may include ECG changes, loss of device detection of post shock electrograms, loss of ability to capture for pacing following shock, short and long term changes in defibrillation threshold, and post shock changes in myocardial contractility (*e.g.*, measured from contour of ventricular pressure curve).

c. Efficacy testing may include proof of optimal function including the following:

i. Recognition of different arrhythmias (where such testing is feasible).

ii. Appropriate therapy for each arrhythmia.

Report of animal testing should include the documentation of compliance with good laboratory practices (GLP), animal care, objective, hypothesis, test procedures, data collection, analysis plan, and a summary of the results. The summary of the results should include an analysis explaining the significance of the results.

III. Clinical Evaluation

ICD development and approval involves evidence of safety and effectiveness gathered during preclinical, pre-approval clinical, post approval reporting, and postmarket surveillance studies. The approval of the beginning of human investigation (IDE approval) and the approval for commercial sale (PMA or PMA supplement approval) are simply two points on the development time-line.

The agency is committed to integrating these premarketing and postmarketing activities. The agency is thus supportive of development plans which include earlier introduction into clinical studies and earlier PMA approval, provided such development plans are rational, safe, and provide the necessary clinical evidence. This includes PMA supplements with adequate preclinical data and appropriate postmarketing studies which could be approved without premarketing clinical studies.

Greater specificity and predictability for the clinical study requirements is one of the primary goals of this guidance. Although there are many possible assumptions and designs, the anticipated ICD changes, both evolutional and novel issues, can be reasonably well defined. In particular, for a given specific ICD, Indication, and clinical claim (equivalence or superiority) we can arrive at an appropriate design.

Table 2 (Appendix G) contains a number of specific designs for specific indications. The associated study design work sheets (one for the premarket study and one for postmarket study) illustrate the approach to developing these specific suggestions.

Following the convention established by Meinert [7] and others, the term **clinical trial** refers to a concurrent control clinical study. The special case where the treatment or control are assigned by randomization defines the **randomized clinical trial (RCT)**. The less restrictive term, **clinical study**, will include clinical trials or any non-concurrent control evaluation of a treatment.

A. Clinical (premarketing) Studies

The FDA must rely on valid scientific evidence to determine whether there is reasonable evidence of a device's safety and effectiveness (21 CFR 860.7(c)). Table 1 portrays preclinical, clinical (premarket), and postmarket surveillance requirements based on the clinical and technology attributes of the ICD change. Specifics of study design will depend on study objectives and endpoints.

Table 2 and the associated work sheets (Appendix G) show examples of some of specific clinical trial designs.

The following briefly discusses the requirements for premarket clinical studies. Further detail is included in Appendix A - Clinical Trial Design, Appendix B - Clinical Data Requirements, Appendix C - Reporting of the Clinical Trial, and Appendix E - Mortality Definitions.

An **Overall Clinical Plan** (about one page) should be prepared initially and updated as necessary. The Clinical Plan should include a brief description (not a complete protocol) of each of the anticipated clinical studies. The sponsor should also make a statement to indicate that appropriate postmarket studies will be conducted to monitor product performance.

The Clinical Plan should include for each study: a descriptive title, the study design including whether concurrent or non-current controls will be used, the primary outcome measures, the number of patients exposed, and the salient results (achieved or expected). (see Appendix A.1) Taken together, these studies should provide the evidence of safety and effectiveness and the basis for the labeling of the device.

Study observations and outcome measures may include, but are not limited to, mortality, number of observations and complications (see Appendix B-4 for definitions), number of successfully treated VT or VF events, inappropriate shocks, therapy response times, and detection efficacy. The **primary outcome measure** will depend on the study design, but mortality should always be assessed and appropriately detailed information should be included for every patient death. Subclasses of mortality should also be provided including sudden cardiac, nonsudden cardiac, or non- cardiac (see Appendix E for mortality definitions).

The number of patients and institutions for given phases of the study will, of course, depend on the study endpoints and study design. The study size should, in all cases, be based on (and

Table 2 (Appendix G) contains a number of specific designs for specific indications. accompanied by) a statistical power calculation and rationale as to study site recruitment.

Section IV of this document sets out guidance concerning when an IDE, original PMA, and PMA supplement would be required for an ICD.

When does an ICD PMA Supplement Require a Clinical Study? Although an original PMA for an ICD requires clinical data, a PMA supplement may not. For example, when the modifications can be qualified on the "bench", e.g., new components, downsized version of an existing device and certain software changes that do not affect detection or therapy, then clinical demonstration may not be required (see table 2 in Appendix G).

However, when a PMA supplement includes new indications for use or device modifications which clearly impact device performance and thus patient treatment, a clinical study will be required. Such modifications may include "new" sensing and detection algorithms, "new" defibrillation waveforms and pathways, or new detection/therapy software capabilities.

B. Post approval Reports

Continued approval of the PMA is contingent upon the submission of post approval reports required under 21 CFR 814.84 at intervals of 1 year from the date of approval of the original PMA. In addition to the information required under the regulation, and in order to provide continued reasonable assurance of the safety and effectiveness of the device for its intended use, the annual post approval reports shall include, separately for each model number (if applicable), the following information known by or reported to the applicant:

1) The number of pulse generators domestically implanted and the number of reported explants and deaths.

2) A breakdown of the reported deaths into pulse generator related and non-pulse generator related.

3) A breakdown of the reported explants into the numbers reported at end of battery life, having complications unresolvable by programming and for other reasons with safety and effectiveness issues which can be derived from the reports stated.

4) The number of pulse generators returned to the applicant for cause from domestic sources with a breakdown into the numbers currently in analysis, operating properly, at normal battery depletion and failed, with the failure mechanisms described.

5) A cumulative survival table for the pulse generators.

6) The number of programmers and modules shipped and the number of returns with a breakdown into the numbers currently in analysis, operating properly and failed, with the failure mechanisms described.

7) Literature references to studies or observations in which the devices is cited.

C. Required Postmarket Surveillance

Under section 522(a) of the Food, Drug, and Cosmetic Act, manufacturers of certain types of devices identified by the Act, or designated by FDA, are to conduct required postmarket surveillance (RPS) studies. FDA has identified **ICDs as requiring postmarket surveillance** under section 522(a)(1)(A). RPS is required of all manufacturers of ICDs who receive **approval of an original PMA or PMA supplement after November 8, 1991,** according to the general outline in Table 1, Section I and specific suggestions in Table 2, Appendix G.

ICDs have been identified as needing Required Postmarket Surveillance because they are permanent implants, the failure of which can cause serious adverse health consequences or death. The specific characteristics of ICDs have necessitated a more **rigorous approach** than previously found acceptable for pacemaker pulse generators. These characteristics include: recent revolutionary changes in technology; likelihood of death as a result of clinical ineffectiveness or hardware/software defect; need for clinical assessment in the general population under actual conditions of use of lead failure/complication and generator complications; and the need to get reasonable numbers of generators interrogated and explanted from deceased patients.

Within thirty (30) days of first introduction or delivery for introduction of this device into interstate commerce, the manufacturer is required to submit to FDA certification of the date of introduction into interstate commerce, a detailed protocol that describes the postmarket surveillance study, and a detailed profile of the study's principal investigator that clearly establishes the qualifications and experience of the individual to conduct the proposed study. General guidance entitled "Draft Guidance to Manufacturers on the Development of Required Postmarket Surveillance Study Protocols under Section 522(a)(1) of the Federal Food, Drug, and Cosmetic Act" is sent with each premarket clearance letter for affected devices.

In addition to the general guidance cited above, this particular document contains device-specific guidance is an effort to help manufacturers by describing a study approach that CDRH would find acceptable.

Each manufacturer's RPS for an ICD should have the following overall objectives:

a. To provide statistically **valid patient and device survival data** for generators and leads (grouped by technical and/or clinical applications) implanted in the general population under actual conditions of use

b. To **provide an early warning system** for the identification of hardware and software failures in ICD systems implanted in the general population under actual conditions of use once a model for acceptable performance is generated and validated in the future by multiple manufacturers

Appendix D contains a draft of the RPS guidance for ICDs.

D. Product Labeling

The *Draft DCRND Device Labeling Guidance* [11] outlines the recommendations to DCRND reviewers concerning the development of labeling for device marketing submissions, especially premarket approval applications (PMAs). The most recently approved ICDs will generally provide the best, current description of appropriate labeling. This document [11] includes examples of labeling from recently approved ICDs.

IV. Type of Application

A. When is an Original Investigational Device Exemption (IDE) Required?

FDA must rely on valid scientific evidence to determine whether there is reasonable evidence of a device's safety and effectiveness (21 CFR 860.7 (c)). In determining the safety and effectiveness of a device, FDA considers (21 CFR 860.7 (b)):

1) the patient population for which the device is intended

2) all conditions for use of the device, including those recommended or suggested in the labeling or advertising

3) the probable benefit from the use of the device weighed against any probable injury or illness from such use

4) the reliability of the device (21CFR 860.7(b)).

This valid scientific evidence should demonstrate the safety and effectiveness of the device and as defined in Section 860.7 may include:

- Well-controlled investigations
- Partially controlled studies
- Studies without matched controls
- Well-documented case histories
- Reports of significant human experience

Section 21 CFR 860.7 (c) (2) and ODE Blue Book Memorandum P91-1 [12] establish that the clinical trial should provide reasonable assurance that the use of the device will provide a clinically significant outcome (clinical utility).

Prior to studying a device which is considered to be a "significant risk" device, as defined per 21 CFR 812.3 (m), the manufacturer (sponsor) should submit an IDE application to FDA. Sherertz, *et al,* report their experience with interpretation of these issues [13]. The IDE should be approved by both FDA and the Institutional Review Board (IRB) before the trial can begin at that institution. The required contents of an IDE application are outlined in 21 CFR 812.20 (b) and on the "Original IDE Review Form".

Thus, each ICD studied in humans should take place under an IDE.

B. When is an IDE Supplement Required?

Changes for which an IDE supplement is required are stated in 21 CFR 812.35. An IDE supplement is required when:

- There are modifications to the device under study
- Incidents concerning the device under study
- Modifications in the study itself.

Annual or periodic study reports, adverse events, study protocol changes, device modifications, additional patient requests, and additional facility requests could all be submitted as a supplement to an IDE.

C. When is an Original Premarket Approval Application (PMA) required?

A premarket approval (PMA) application is the presentation and analysis of clinical data collected under the IDE application, along with other information required under 21 CFR 814.20, such as an extensive description of the manufacturing procedures and device experience outside the United States. The presentation and analysis of the clinical data comprise a significant portion of the Summary of Safety and Effectiveness Data (SSED) which is made available to the public after device approval. The SSED is written to include all aspects of the device testing, including *in vitro*, animal, and clinical testing, and is FDA's summary basis of approval (the FDA's determination that the device is reasonable safe and effective), and can be granted approval for market release.

The determination of safety and effectiveness is based principally on four factors, as outlined in 21 CFR 860.7:

1 - Persons for whom the device is intended

2 - Conditions for use of the device, including conditions for use prescribed, recommended, or suggested in the labeling or advertising of the device, or other intended conditions for use

3 - Probable benefit from the use of the device weighed against any probable injury or illness from such use

4 - Reliability of the device [14].

The PMA regulation describes the content and format of a PMA application, as well as the requirements for subsequent submissions (e.g., supplements and progress reports). Only pertinent issues relating to ICD devices are presented here.

Before initiation of the clinical study, the sponsor should clearly identify the research question(s) to be answered by the data from the clinical trial. There should be sufficient valid scientific evidence to support the intended labeling claims for the device and demonstrate the safety, effectiveness, and clinical utility of the device.

The sponsor should consider the following points when making this determination and preparing the PMA application:

1 - Do the data support the indications?

2 - Have the proper statistical methods been used based upon the study design?

3 - Have the data been correctly compared to the appropriate control population regarding inclusion criteria, success and failure rates, morbidity and mortality?

4 - Does the use of the device offer benefit(s) to the patient which outweighs the risks?

Sponsors of PMA applications should follow the format as outlined in 21 CFR 814.20 and discussed in the "Premarket Approval (PMA) Manual". This and a number of other helpful documents are available from Division of Small Manufacturers Assistance (DSMA) 800-638-2014.

An Original PMA is required for any first submission of an ICD or any novel design (see Section I, Table 1).

D. When is a PMA Supplement Required?

A PMA supplement can be submitted instead of an original PMA when the modifications to the PMA approved ICD do not raise new or different safety or effectiveness issues. As summarized in Table 1 (Section I), technology changes which are evolutional (as opposed to novel) may be appropriately handled as a PMA supplement .

A PMA supplement is thus required (21 CFR 814.39) when:

1. "Unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification; or "
2. "The device is to be modified and the modified device should be subjected to animal or laboratory or clinical testing designed to determine if the modified device remains safe and effective." [15]

E. When is Panel Involvement/Review Required?

SMDA 90 provided the agency increased discretion in bringing devices before the panels. Blue Book Memo P91-2 of 5/13/91 admonishes ODE reviewers to "take all measures required to eliminate unnecessary panel involvement in the evaluation of PMAs." [16]. The three criteria for recommending a PMA be submitted for panel reviewed are:

1. Lack of knowledge or experience to evaluate the safety or effectiveness without panel input
2. The PMA raises a new issue best addressed by the panel, or
3. The data establishing the clinical performance reveal unanticipated safety and efficacy questions.

The panel has an added value to DCRND's review process in

1. Providing a careful, competent consideration of new clinical issues. The panel can, and should, offer for agency consideration, all sides of a controversial issue. The DCRND review team should work with the panel chairperson and executive secretary to make certain that all sides of such controversies are represented at the panel meeting.
2. Provide a public forum for the open discussion of new and controversial issues.
3. Develop the multidisciplinary review and refinement of product labeling, both format and content.

See *DCRND Panel Referral Decision - Draft Guidance* for details.

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38. Poole et al., "Serial Defibrillation Threshold Measures in Man: A Prospective Controlled Study", Journal of Cardiovascular Electrophysiology", 6(1) January 1995, p. 19. Abstract: A one year study confirming a transient rise in post-implant DFT, suggesting changes in the electrode-tissue interface.

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39. Vester et al., "Efficacy and long term stability of a single endocardial lead configuration for permanent implantation of cardioverter defibrillators", PACE 16, April 1993, #101, p. 875.

40. Schwartzman et al., "Rise in defibrillation threshold early after implantation of nonthoracotomy defibrillation lead systems: Incidence and predictors", J. American College of Cardiology, February 1994, #726-3, p 112A.

41. Carlson et al., "Initial experience with a transvenous implantable cardioverter defibrillation system using a biphasic shock", J. American College of Cardiology, February 1994, #726-5, p 112A.

42. Tummala et al., "Chronic changes in defibrillation parameters with a transvenous lead system", J. American College of Cardiology, February 1994, #726-6, p 112A.

43. Venditti et al., "Rise in defibrillation threshold in transvenous ICD using a biphasic waveform", PACE 17, April 1994, #379, p. 836.

44. Pitschner et al., "Long term stability of nonthoracotomy defibrillation thresholds", PACE 17, April 1994, #380, p. 836.

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49. Bardy et al., "Subacute changes in defibrillation threshold following multiprogrammable defibrillator implantation in man", J American College of Cardiology 17(2) February 1991, p. 344A.

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METHODS / STATISTICS

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VI. Appendices

Appendix A. Clinical Study Design

The study design should be based upon a well-defined, clear question or set of questions concerning the device, that are to be answered by the clinical study [17-23]. The design of a prospective trial should yield a written clinical plan or protocol which, when followed, will answer the question(s) with a defined degree of precision.

The success of the clinical trial depends on the study design, study conduct, data analysis, and the appropriate inferences, it is recommended that a team be established by the sponsor to coordinate these aspects of the study and assure compliance with the study protocol. In addition, the sponsor should consider including a Data and Safety Monitoring Board and an Events (Endpoint) Committee to provide an unbiased (ideally blinded) assessment of the primary outcome measures.

1. The Overall Clinical Plan - The Clinical Plan should briefly describe each clinical study planned to be a part of the product development. The Clinical Plan is not a collection of study protocols, but a brief (one page) overview of the expected patient exposure and results. The Clinical Plan should include for each study:

- descriptive title
- study design including whether concurrent or non-current controls will be used
- sample size
- primary outcome measures
- salient results (achieved or expected)

Taken together, these studies should provide the sufficient valid scientific evidence of safety and effectiveness and the basis for the labeling of the device.

When more than one page is required to provide this information, a one-page summary should be prepared as well.

2. The Study Protocol - We will first consider general protocol design considerations and then discuss the design issues specific to ICDs.

a. General Protocol Considerations

Although there are many approaches to the structure of the study protocol), the eight-point structure which follows, adapted from Hirsh [24], has much to recommend it.

- **Objective:** What are you after?
  - State your **specific aims** -- a brief, specific statement of what you hope to accomplish with this activity.
  - Clearly delineate the **study hypotheses**.

- **Study design:** Has the most efficient study design been chosen to address the objective?
  - State the **study type** (open study, concurrent control, parallel, cross-over, randomized, ...).
  - If not a randomized concurrent control, **explicitly identify your control group.**
  - If you are relying on historical controls, identify the data and support their similarity to your study population.
  - **Define your PRIMARY ENDPOINT** (or measures) and make sure they're clinically relevant.
  - **Define your SECONDARY ENDPOINTS.**
  - Explicitly state your plans to **maximize PATIENT SAFETY** and what you will measure to verify each patient's well-being.
- **Study sample** Are the right patients being studied?
  - **State your INCLUSION CRITERIA** -- circumscribe the patient population to be studied.
  - **State your EXCLUSION CRITERIA** -- remove the patients you wish excluded from the population to be studied.
  - Specify the **size of your study groups** (N) including the expected completion (dropout) rate . Study size should be adequate to address the study hypotheses (adequately powered study).
  - Specify **how many centers** will be involve- Specify a maximum and minimum number of patients per center.
- **Assignment:** How will patients be assigned to the study and control groups?
  - If the study is a randomized clinical trial, assure that the **randomization is BLINDED** (patient, care-giver, and evaluator) as far as possible.
  - Regardless of the study type, **assure comparable study and control groups** with respect to characteristics other than the study factor(s).
- **Assessment**: How will the best measures of your primary and secondary endpoints be obtained?
  - Your **patient consent form** should communicate all important issues to the patient.
  - The **measure of each endpoint should be as accurate and precise** as you can make it.
  - **Specify when you will make each measurement** (and the allowable window).
  - Your case report form (**CRF) should capture all clinically important** safety and efficacy measures.
  - Minimize (and assess) the impact of the process of observation on the outcome.
- **Analysis:** Did the analysis properly compare the outcomes in the study and the control groups?
  - Your **ANALYSIS PLAN** should detail both descriptive (plentiful) and inferential analyses (appropriately), any necessary algorithms, how missing data will be handled, how interactions and covariates will be examine- The detail should be such that a professional statistician given the Analysis Plan + a data disk, could reach the same answers
  - Assess the similarity (**lack of apparent bias) in the treatment and control groups** (especially if historical controls are used)

- Assess (or adjust) your results for the **effect of possible confounding variables.**
- Be sure your statistical significance tests (**inferential statistics) are properly applied.**
- Use a **point estimate and 95% confidence limit** (two-tailed p-values) where ever appropriate (all most always).

• **Interpretation:** What conclusions are expected from the investigation for the patients included in the study group?

- Shoot for an effect size (in the case of the null hypothesis) which is **clinically meaningful** or important.
- Shoot for an maximum difference (for equivalence hypothesis) which is **clinically insignificant** or unimportant.

• **Extrapolation:** What extrapolations to individuals and situations not included in the study will be made?

- Consider both the **relative risk and absolute risk** when extrapolating to individuals.
- When extrapolating to new groups with the risk factor, take into account **the attributable risk percentage.**
- When **extrapolating to the new groups** composed of individuals with and without the risk factor, take into account the population attributable risk percentage.
- Avoid extrapolation beyond the domain of the data.
- Consider differences between the study group and the target population.

b. Protocol Considerations Specific to ICDs

Description of Control Groups - Every ICD study has an explicit or implicit control group. For an "observational study", the control group is implicit. The protocol should clearly define the experimental and control group for the study. Include information on the type of device/ lead system used in each group, as well as any other treatment differences between groups. The type of control used should be clearly stated and the rationale for the choice of this control should be given.

Baseline Variables - Identify the demographic and clinically significant baseline variables to be assessed in order to properly select patients for the device and to ensure comparability of the patients within the cohort and to the control group. One of the greatest limitations in use of non-RCT studies is the difficulty in matching the baseline characteristics of the new and control patient groups. Variables should be clearly and concisely defined, and measurable by standard and objective methods.

The primary outcome measure(s) may not include mortality, but mortality should always be assessed and appropriately detailed information should be included for every patient death. Subclasses of mortality may also be provided; however, study design estimates should be based on predictions of total mortality. Subclasses of mortality should be sudden cardiac, nonsudden cardiac, or non- cardiac.

• Duration of Study - The expected duration of the study should be declared and should allow for sufficient data to be gathered to meet the proposed study objectives.

• Protocol - Describe the methodology to be used and provide an assessment of the scientific soundness of the study by addressing the following items:

- Description of Patient Populations
  - Inclusion/Exclusion Criteria - Precisely state the criteria used for patient selection. The criteria should be stated using standard definitions, be consistent with study objectives, and be strictly adhered to by the investigators. If a patient does not meet these criteria, but are nonetheless treated, the circumstances should be described and the patient followed for the duration of the study.
  - If a multi-center trial is planned, pool ability should be justified.
  - Issues of Gender/Racial Bias - FDA's mission actively supports the inclusion of women and minorities in clinical studies. As a result, gender and racial bias issues should be addressed within the IDE application. This issue can be addressed by answering the following two questions:
    1) Is the selection ratio of men to women, or the predominance/omission of a racial/ethnic group reflective of the underlying distribution of the disease for that study population; what methods are in place to control for the selection bias on the basis of gender or race/ethnicity?
    2) Will proposed data analyses address any differences in the safety and effectiveness of the device based on gender (i.e., was the device more or less effective in sub populations)?

When it is not possible to perform quantitative statistical analysis on gender or racially stratified data, because too few patients are assigned to each strata to provide statistical significance when individually assessed, a more qualitative analysis of trend can be performed.

Specific definitions of success, failure, observations and complications (major and minor) should be established prior to initiating the study and specified in the protocol. They should be used without change during patient enrollment and data analysis. The study should be evaluated on the basis of carefully defined criteria, which should be accurate and fit the goals of the trial.

3. Methodology - Methods regarding the generation and collection of data should be provided. Data collection methods should be grouped by follow-up times. Copies of data collection forms should be provided as an appendix to the IDE application. Reasons for an acceptable deviation from the trial methodology should be listed. A complete description of the follow-up methods should be provided in the IDE application. List all times when follow-up data are collected. It is recommended that follow-up times be at predischarge, then every 3-4 months thereafter or as clinically indicated. List the data elements and procedures used to collect the data. For examples of follow-up data collection and methods (see Appendix B).

4. Statistical Methods - Justification of Sample Size and Number of Sites - A calculation of sample size showing all aspects of the chosen sample size formula should be provided. All factors of the equation should be clearly listed.

If historical information is used, such as an event probability taken from one or more other studies, the source of this information should be clearly cited. The source of the chosen statistical formula used to calculate the sample size should also be clearly cited.

Confidence intervals (CIs) can (and in most cases do) improve the representation of information from clinical trials [25]. This is especially true where proportions are concerned and where the point estimate is near 0 or 100%. DCRND expects to see an increasing use of relative risk estimates and CIs in reports of clinical trials reviewed.